OIPE JC169
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PATENT & TRADEMARK OFFICE

Amendments to the Specification:

Please replace the heading beginning on page 192, line 18, with the following amended heading:

Example [[97]] 95

Please replace the paragraph bridging pages 192 and 193 with the following amended paragraph:

Hydrogen chloride was bubbled through a solution of ethyl N-[4-(1-t-butoxycarbonylpiperidin-4-yloxy)phenyl]-N-[3-(3-cyanophenyl)-2-fluoro-2-(Z)-propenyl]sulfamoylacetate (1.41 g) obtained in reference example ~~131~~ 128 in a mixture of dichloromethane (25 ml) and ethanol (25 ml) under ice-cooling, and the resulting mixture was stirred at room temperature for 10 hours under sealed conditions and then evaporated in vacuo. Subsequently, to a solution of the residue obtained in ethanol (30 ml) were added successively an aqueous ammonium chloride solution (prepared by dissolving 0.25 g in 10 ml of water) and a 28 % ammonia solution (0.47 ml), and the resulting mixture was allowed to stand at room temperature for 8 hours. After standing, to the reaction mixture was added a 4N solution of hydrogen chloride in dioxane (1 ml) and the resulting mixture was evaporated in vacuo. The residue obtained was purified by preparative HPLC (YMC-Pack ODS-A; YMC, eluent: 20 % acetonitrile/water) to afford the title compound (1.00 g, yield: 75 %) as a colorless amorphous solid.

Please replace the heading beginning on page 193, second line from the bottom, with the following amended heading:

Example [[98]] 96

Please replace the first full paragraph which begins on line 3 of page 194 with the following amended paragraph:

Ethyl N-[3-(3-amidinophenyl)-2-fluoro-2-(Z)-propenyl]-N-[4-[1-(4,5-dihydro-3H-pyrrol-2-yl)piperidin-4-yloxy]phenyl]sulfamoylacetate dihydrochloride (0.47 g) obtained in example ~~97~~ 95(b) was dissolved in 3N hydrochloric acid (20 ml) and the resulting mixture was stirred at 70°C for 2.5 hours. After cooling to room temperature, the reaction mixture was evaporated in vacuo. The residue obtained was purified by preparative HPLC (YMC-Pack ODS-A; YMC, eluent: 15 % acetonitrile/water). The amorphous solid obtained was dissolved in 1N hydrochloric acid (2.5 ml), and the resulting mixture was evaporated to dryness in vacuo to afford the title compound (0.39 g, yield: 86 %) as a colorless amorphous solid.

Please replace the heading beginning on page 194, line 18, with the following amended heading:

Example **[[99]]** 97

Please replace the last paragraph on page 194, which begins on line 10 from the bottom, with the following amended paragraph:

Hydrogen chloride was bubbled through a solution of ethyl N-[4-(1-t-butoxycarbonylpiperidin-4-yloxy)-3-carbamoylphenyl]-N-[3-(3-cyanophenyl)-2-fluoro-2-(Z)-propenyl]sulfamoylacetate (4.30 g) obtained in reference example ~~132~~ 129 in a mixture of dichloromethane (35 ml) and ethanol (35 ml) under ice-cooling, and the resulting mixture was stirred at room temperature for 3 hours under sealed conditions and then evaporated in vacuo. Subsequently, to a solution of the residue obtained in ethanol (30 ml) were added successively an aqueous ammonium chloride solution (prepared by dissolving 0.80 g in 5 ml of water) and a 28 % ammonia solution (1.80 ml), and the resulting mixture was allowed to stand at room temperature overnight and then evaporated in vacuo.

Please replace the heading on page 195, fourth line from the bottom, with the following amended heading:

Example [[100]] 98

Please replace the first paragraph on page 196 with the following amended paragraph:

Ethyl N-[3-(3-amidinophenyl)-2-fluoro-2-(Z)-propenyl]-N-[3-carbamoyl-4-[1-(4,5-dihydro-3H-pyrrol-2-yl)piperidin-4-yloxy]phenyl]sulfamoylacetate (0.27 g) obtained in example ~~99~~ 97(b) was dissolved in 3N hydrochloric acid (20 ml) and the resulting mixture was stirred at 70°C for 2.5 hours. After cooling to room temperature, the reaction mixture was evaporated in vacuo. The residue obtained was purified by preparative HPLC (YMC-Pack ODS-A; YMC, eluent: 10 % acetonitrile/water). The amorphous solid obtained was dissolved in 1N hydrochloric acid (1.2 ml), and the resulting mixture was evaporated to dryness in vacuo to afford the title compound (0.20 g, yield: 77 %) as a colorless amorphous solid.

Please replace the heading beginning on page 196, line 16, with the following amended heading:

Example [[101]] 99

Please replace the paragraph bridging pages 196 and 197 with the following amended paragraph:

Hydrogen chloride was bubbled through a solution of N-[4-(1-t-butoxycarbonylpiperidin-4-yloxy)-3-carbamoylphenyl]-N-[3-(3-cyanophenyl)-2-(E)-propenyl]methanesulfonamide (1.01 g) obtained in reference example ~~134~~ 131 in a mixture of dichloromethane (7.5 ml) and ethanol (7.5 ml) under ice-cooling, and the resulting mixture was stirred at room temperature for 4 hours under sealed conditions and then evaporated in vacuo. Subsequently, to a solution of the residue obtained in ethanol (15 ml) were added successively an aqueous ammonium chloride solution (prepared by dissolving 0.24 g in 3 ml of water) and a 28 % ammonia solution (0.43 ml), and the resulting mixture was allowed to stand at room temperature overnight and then evaporated in vacuo. To the residue obtained were added successively ethanol (10 ml) and a 4N solution of hydrogen chloride in dioxane (2 ml), and the resulting mixture was evaporated in vacuo. The residue obtained was purified by preparative HPLC (YMC-Pack ODS-A; YMC, eluent: 10 % acetonitrile/water). Subsequently, to a solution of the amorphous solid obtained in ethanol (10 ml) was added a 4N solution of hydrogen chloride in dioxane (2 ml), and the resulting mixture was evaporated to dryness in vacuo. The residue obtained was dissolved in water and then lyophilized to afford the title compound (0.95 g, yield: 98 %) as a pale yellow amorphous solid.

Please replace the paragraph beginning on page 197, line 14, with the following amended paragraph:

To a solution of N-[3-(3-amidinophenyl)-2-(E)-propenyl]-N-[3-carbamoyl-4-(piperidin-4-yloxy)phenyl]methanesulfonamide dihydrochloride (0.95 g) obtained in example ~~101~~ 99(a) in ethanol (15 ml) were added successively 5-methoxy-3,4-dihydro-2H-pyrrole (0.52 g), which was prepared from 2-pyrrolidinone according to the method described in Org. Prep. Proced. Int., 24, 147 (1992), and triethylamine (1.20 ml) at room temperature, and the resulting mixture was allowed to stand at room temperature overnight, and at the end of this time, 5-methoxy-3,4-dihydro-2H-pyrrole (0.17 g) and triethylamine (0.24 ml) were furthermore added successively, and the resulting mixture was stirred at room temperature for 6 hours and then evaporated in vacuo. Subsequently, to the residue obtained were added successively ethanol (10 ml) and a 4N solution of hydrogen chloride in dioxane (4 ml), and the resulting mixture was evaporated in vacuo. The residue obtained was purified by preparative HPLC (YMC-Pack ODS-A; YMC, eluent: 10 %

acetonitrile/water). The amorphous solid obtained was dissolved in 1N hydrochloric acid (5 ml), and the resulting mixture was evaporated to dryness in vacuo. The residue obtained was dissolved in water and then lyophilized to afford the title compound (0.67 g, yield: 63 %) as a colorless amorphous solid.

Please replace the heading on page 198, line 2, with the following amended heading:

Example [[102]] 100

Please replace the paragraph beginning on page 198, line 8, with the following amended paragraph:

Hydrogen chloride was bubbled through a solution of N-[4-(1-t-butoxycarbonylpiperidin-4-yloxy)-3-carbamoylphenyl]-N-[3-(3-cyanophenyl)-2-(E)-propenyl]ethanesulfonamide (1.08 g) obtained in reference example ~~135~~ 132 in a mixture of dichloromethane (8 ml) and ethanol (8 ml) under ice-cooling, and the resulting mixture was stirred at room temperature for 4 hours under sealed conditions and then evaporated in vacuo. Subsequently, to a solution of the residue obtained in ethanol (16 ml) were added successively an aqueous ammonium chloride solution (prepared by dissolving 0.26 g in 3 ml of water) and a 28 % ammonia solution (0.46 ml), and the resulting mixture was allowed to stand at room temperature overnight and then evaporated in vacuo. To the residue obtained were successively added ethanol (10 ml) and a 4N solution of hydrogen chloride in dioxane (2 ml) and the resulting mixture was evaporated in vacuo. The residue obtained was purified by preparative HPLC (YMC-Pack ODS-A; YMC, eluent: 10 % acetonitrile/water). Subsequently, to a solution of the amorphous solid obtained in ethanol (10 ml) was added a 4N solution of hydrogen chloride in dioxane (2 ml), and the resulting mixture was evaporated to dryness in vacuo to afford the title compound (0.68 g, yield: 64 %) as a pale yellow amorphous solid.

Please replace the paragraph bridging pages 198, and 199 with the following amended paragraph:

To a solution of N-[3-(3-amidinophenyl)-2-(E)-propenyl]-N-[3-carbamoyl-4-(piperidin-4-yloxy)phenyl]ethanesulfonamide dihydrochloride (0.68 g) obtained in example ~~102~~ 100(a) in ethanol (15 ml) were added successively 5-methoxy-3,4-dihydro-2H-pyrrole (0.36 g), which was prepared from 2-pyrrolidinone according to the method described in Org. Prep. Proced. Int., 24, 147 (1992), and triethylamine (0.85 ml) at room temperature and the resulting mixture was allowed to stand at room temperature overnight. At the end of this time, to the reaction mixture were furthermore added successively 5-methoxy-3,4-dihydro-2H-pyrrole (0.19 g) and triethylamine (0.34 ml) at room temperature, and the resulting mixture was stirred at room temperature for 5 hours and then evaporated in vacuo. Subsequently, to the residue obtained were successively added ethanol (10 ml) and a 4N solution of hydrogen chloride in dioxane (4 ml), and the resulting mixture was evaporated in vacuo. The residue obtained was purified by preparative HPLC (YMC-Pack ODS-A; YMC, eluent: 10 % acetonitrile/water). To the amorphous solid obtained was added 1N hydrochloric acid (8 ml) and the resulting mixture was evaporated to dryness in vacuo. The residue obtained was dissolved in water and then lyophilized to afford the title compound (0.56 g, yield: 73 %) as a pale brown amorphous solid.

Please replace the heading beginning on page 199, line 24, with the following amended heading:

Example [[103]] 101

Please replace the last paragraph bridging pages 199 and 200 with the following amended paragraph:

To a solution of N-[3-(3-amidinophenyl)-2-(E)-propenyl]-N-[3-carbamoyl-4-(piperidin-4-yloxy)phenyl]methanesulfonamide (0.32 g) obtained in example ~~101~~ 99(a) in methanol (15 ml) were added successively 2-ethoxy-4,5-dihydrooxazole (0.21 g), which was prepared from 2-oxazolidone according to the method described in Eur. J. Org. Chem., 10, 2645 (1999), and triethylamine (0.56 ml) at room temperature, and the resulting mixture was stirred at room temperature for 2 hours and allowed to stand at room temperature overnight and then evaporated in vacuo. The residue obtained was purified by preparative HPLC (YMC-Pack ODS-A; YMC, eluent: 12 % acetonitrile/water). The amorphous solid obtained was dissolved in 1N hydrochloric acid (1.2 ml) and evaporated to dryness in vacuo to afford the title compound (0.15 g, yield: 59 %) as a colorless amorphous solid.

Please replace the heading on page 200, line 9 with the following amended heading:

Example [[104]] 102

Please replace the paragraph beginning on line 13 on page 200 with the following amended paragraph:

To a solution of N-[3-(3-amidinophenyl)-2-(E)-propenyl]-N-[3-carbamoyl-4-(piperidin-4-yloxy)phenyl]methanesulfonamide (0.32 g) obtained in example ~~101~~ 99(a) in a mixture of tetrahydrofuran (3 ml), 1,4-dioxane (3 ml) and water (3 ml) were added successively 2-chloroisothiocyanate (0.05 ml) and triethylamine (0.07 ml) under ice-cooling, and the resulting mixture was stirred at room temperature for 1.5 hours and allowed to stand at room temperature overnight and then evaporated in vacuo. The residue obtained was purified by preparative HPLC

(YMC-Pack ODS-A; YMC, eluent: 12 % acetonitrile/water). The amorphous solid obtained was dissolved in 1N hydrochloric acid (1.2 ml) and evaporated to dryness in vacuo to afford the title compound (0.15 g, yield: 59 %) as a colorless amorphous solid.

Please replace the heading beginning on page 200, line 5 from the bottom, with the following amended heading:

Example [[105]] 103

Please replace the heading on page 201, line 3 from the bottom, with the following amended heading:

Example [[106]] 104

Please replace the heading on page 202, line 3 from the bottom, with the following amended heading:

Example [[107]] 105

Please replace the heading on page 206, line 20 with the following amended heading:

Example [[108]] 106

Please replace the heading on page 204, line 20 with the following amended heading:

Example [[109]] 107

Please replace the paragraph bridging pages 204 and 205 with the following amended paragraph:

To a solution of N-[3-(3-amidinophenyl)-2-(E)-propenyl]-N-[3-carbamoyl-4-[1-(4,5-dihydro-3H-pyrrol-2-yl)piperidin-4-yloxy]phenyl]methanesulfonamide dihydrochloride (0.23 g) obtained in example ~~101~~ 99(b) in a mixture of dichloromethane (4.5 ml) and N,N-dimethylformamide (1.5 ml) were added successively ethyl 4-nitrophenyl carbonate (0.10 g) obtained in example ~~105~~ 103 and triethylamine (0.16 ml) at room temperature, and the resulting mixture was stirred at room temperature overnight and then evaporated in vacuo. The residue obtained was purified by chromatography on a silica gel column using a mixed solvent of dichloromethane and methanol (50:0 ~ 47:3). Subsequently, to a solution of the oily product obtained in ethanol (2 ml) was added a 4N solution of hydrogen chloride in dioxane (0.5 ml), and the resulting mixture was evaporated to dryness in vacuo. The amorphous solid obtained was dissolved in dichloromethane, and the resulting mixture was extracted with 1N hydrochloric acid, and the aqueous layer collected was evaporated in vacuo. The residue obtained was dissolved in water and then lyophilized to afford the title compound (0.20 g, yield: 84 %) as a colorless amorphous solid.

Please replace the heading on page 205, line 10 with the following amended heading:

Example [[110]] 108

Please replace the paragraph beginning on page 205, line 14 with the following amended paragraph:

To a solution of N-[3-(3-amidinophenyl)-2-(E)-propeyl]-N-[3-carbamoyl-4-[1-(4,5-dihydro-3H-pyrrol-2-yl)piperidin-4-yloxy]phenyl]methanesulfonamide dihydrochloride (0.20 g) obtained in example ~~101~~ 99(b) in a mixture of dichloromethane (2.5 ml) and acetonitrile (2.5 ml) were added successively 4-nitrophenyl pivalate (0.09 g) and triethylamine (0.23 ml) with stirring under ice-cooling, and the resulting mixture was stirred at room temperature for 4 hours. After stirring, to the reaction mixture was added dichloromethane, and the organic layer was washed successively with a 1N aqueous sodium hydroxide solution and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and evaporated in vacuo. The residue obtained was purified by chromatography on a silica gel column using a mixed solvent of dichloromethane and methanol (50:0 ~ 47:3) to afford the title compound (0.17 g, yield: 86 %) as a colorless amorphous solid.

Please replace the heading on page 205, line 2 from the bottom with the following amended heading:

Example [[111]] 109

Please replace the paragraph beginning on page 206, line 3 with the following amended paragraph:

To a solution of N-[3-(3-amidinophenyl)-2-(E)-propenyl]-N-[3-carbamoyl-4-[1-(4,5-dihydro-3H-pyrrol-2-yl)piperidin-4-yloxy]phenyl]methanesulfonamide dihydrochloride (0.30 g) obtained in example ~~101~~ 99(b) in a mixture of dichloromethane (4 ml) and acetonitrile (4 ml) were added successively 4-nitrophenyl benzoate (0.15 g) and triethylamine (0.28 ml) with stirring under ice-cooling, and the resulting mixture was stirred at room temperature overnight. After stirring, the reaction mixture was diluted with dichloromethane, and the organic layer was washed successively with a 0.5N aqueous sodium hydroxide solution and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and evaporated in vacuo. The residue obtained was purified by chromatography on a silica gel column using a mixed solvent of dichloromethane and methanol (50:0 ~ 47:3). The purified solid obtained was dissolved in water and then lyophilized to afford the title compound (0.24 g, yield: 75 %) as a pale yellow amorphous solid.

Please replace the heading on page 206, line 23 with the following amended heading:

Example [[112]] 110

Please replace the paragraph bridging pages 206 and 207 with the following amended paragraph:

To a solution of N-[3-(3-amidinophenyl)-2-(E)-propenyl]-N-[3-carbamoyl-4-[1-(4,5-dihydro-3H-pyrrol-2-yl)piperidin-4-yloxy]phenyl]methanesulfonamide dihydrochloride (0.29 g) obtained in example ~~101~~ 99(b) in a mixture of dichloromethane (3 ml) and acetonitrile (3 ml) were added successively 4-nitrophenyl acetate (0.09 g) and triethylamine (0.26 ml) with stirring under ice-cooling, and the resulting mixture was stirred at room temperature for 4 hours. After stirring, to the reaction mixture was added dichloromethane, and the organic layer was washed successively with a 0.5N aqueous sodium hydroxide solution and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and evaporated in vacuo. The residue obtained was purified by chromatography on a silica gel column using a mixed solvent of dichloromethane and methanol (50:0 ~ 47:3). The solid obtained was dissolved in water and then lyophilized to afford the title compound (0.16 g, yield: 58 %) as a pale yellow amorphous solid.

Please replace the heading on page 207, line 12 with the following amended heading:

Example [[113]] 111

Please replace the paragraph bridging pages 207 and 208 with the following amended paragraph:

Subsequently, to a solution of N-[3-(3-amidinophenyl)-2-(E)-propenyl]-N-[3-carbamoyl-4-[1-(4,5-dihydro-3H-pyrrol-2-yl)piperidin-4-yloxy]phenyl]methanesulfonamide dihydrochloride (0.29 g) obtained in example ~~101~~ 99(b) in a mixture of dichloromethane (3.5 ml) and acetonitrile (3.5 ml) were added successively (4-methoxyphenyl)(4-nitrophenyl) carbonate (0.15 g) obtained above and triethylamine (0.27 ml), and the resulting mixture was stirred at room temperature for 1.5 hours. After stirring, the reaction mixture was diluted with dichloromethane, and the organic layer was washed successively with a 0.5N aqueous sodium hydroxide solution and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and evaporated in vacuo. The residue obtained was purified by chromatography on a silica gel column using a mixed solvent of dichloromethane and methanol (20:0 ~ 19:1). The purified product obtained was dissolved in water and then lyophilized to afford the title compound (0.23 g, yield: 69 %) as a colorless amorphous solid.

Please replace the heading on page 271, fourth line from the bottom with the following amended heading:

Reference example [[130]] 127

Please replace the heading on page 272, third line from the bottom, with the following amended heading:

Reference example [[131]] 128

Please replace the first paragraph on page 273 with the following amended paragraph:

To a solution of 3-(3-cyanophenyl)-2-fluoro-2-(Z)-propen-1-ol (0.45 g) obtained in reference example ~~130~~ 127 , ethyl N-[4-(1-t-butoxycarbonylpiperidin-4-yloxy)phenyl]sulfamoylacetate (1.12 g) obtained in reference example 107 and triphenylphosphine (0.80 g) in dichloromethane (20 ml), diethyl azodicarboxylate (0.48 ml) was added dropwise with stirring under ice-cooling, and the resulting mixture was stirred at the same temperature for 2 hours and then evaporated in vacuo. The residue obtained was purified by chromatography on a silica gel column using a mixed solvent of dichloromethane and ethyl acetate (15:1) as the eluent to afford the title compound (1.40 g, yield: 92 %) as a colorless oil.

Please replace the heading on page 273, line 14 with the following amended heading:

Reference example [[132]] 129

Please replace the paragraph beginning on page 273, line 17 with the following amended paragraph:

To a solution of 3-(3-cyanophenyl)-2-fluoro-2-(Z)-propen-1-ol (0.80 g) obtained in reference example ~~130~~ 127 , ethyl N-[4-(1-t-butoxycarbonylpiperidin-4-yloxy)-3-carbamoylphenyl]sulfamoylacetate (2.20 g) obtained in reference example 118 and triphenylphosphine (1.50 g) in dichloromethane (50 ml), diethyl azodicarboxylate (0.86 ml) was added dropwise with stirring under ice-cooling, and the resulting mixture was stirred at room temperature for 2.5 hours and then evaporated in vacuo. The residue obtained was purified by chromatography on a silica gel column using a mixed solvent of hexane and ethyl acetate (1:4 ~ 1:2) as the eluent to afford the title compound (3.40 g, quantitative yield) as a pale yellow amorphous solid.

Please replace the heading on page 273, third from the bottom, with the following amended paragraph:

Reference example [[133]] 130

Please replace the heading on page 274, line 24 with the following amended heading:

Reference example [[134]] 131

Please replace the last paragraph on page 274, which begins on line 26, with the following amended paragraph:

To a solution of 3-[3-[N-[4-(1-t-butoxycarbonylpiperidin-4-yloxy)-3-carbamoylphenyl]amino]-1-(E)-propenyl]benzonitrile (0.85 g) obtained in reference example ~~133~~ 130 in dichloromethane (15 ml) were successively added dropwise methanesulfonyl chloride (0.17 ml) and pyridine (0.29 ml) with stirring under ice-cooling, and the resulting mixture was stirred at room temperature overnight. After stirring, to the reaction mixture was added methanol (3 ml), and the resulting mixture was evaporated in vacuo. The residue obtained was purified by chromatography on a silica gel column using a mixed solvent of dichloromethane and methanol (10:0 ~ 9:1) as the eluent to afford the title compound (1.01 g, quantitative yield) as a colorless oil.

Please replace the heading on page 275, line 5 with the following amended heading:

Reference example [[135]] 132

Please replace the paragraph beginning on line 8 of page 275 with the following amended paragraph:

To a suspension of 3-[3-[N-[4-(1-t-butoxycarbonylpiperidin-4-yloxy)-3-carbamoylphenyl]amino]-1-(E)-propenyl]benzonitrile (0.92 g) obtained in reference example ~~133~~ 130 in dichloromethane (15 ml) were successively added dropwise ethanesulfonyl chloride (0.22 ml) and pyridine (0.31 ml) with stirring under ice-cooling, and the resulting mixture was stirred at room temperature overnight. At the end of this time, to the reaction mixture were furthermore added dropwise ethanesulfonyl chloride (0.04 ml) and pyridine (0.16 ml) with stirring under ice-cooling, and the resulting mixture was stirred at room temperature for 5 hours. After stirring, to the reaction mixture was added methanol (3 ml), and the resulting mixture was evaporated in vacuo. The residue obtained was purified by chromatography on a silica gel column using a mixed solvent of dichloromethane and methanol (10:0 ~ 9:1) as the eluent to afford the title compound (1.08 g, yield: 90 %) as a yellow oil.